General

Guideline Title

ACR Appropriateness Criteria® localized nodal indolent lymphoma.

Bibliographic Source(s)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Localized Nodal Indolent Lymphoma

Variant 1: 58-year-old woman with stage IA follicular lymphoma (grade 1 or 2) involving multiple 2 cm lymph nodes in the right cervical neck.

Treatment	Rating	Comments
Chemotherapy alone	2	
Immunotherapy alone	4	
Chemotherapy and immunotherapy	3	
Radioimmunotherapy alone	2	
Chemotherapy and immunotherapy followed by IFRT (24–30 Gy)	4	
Immunotherapy followed by IFRT (24–30 Gy)	4	
Observation	4	

Treatment	Rating	Comments
Radiation Therapy Alone		
24–30 Gy	9	
36–45 Gy	4	Doses >36 Gy carry the potential for toxicity.
4 Gy	4	
Extended field radiotherapy (EFRT)	1	
Involved field radiotherapy (IFRT)	8	
Involved node radiotherapy (INRT)	3	Usually considered after immunotherapy or chemotherapy.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 67-year-old man with stage IIA follicular lymphoma (grade 2) involving the right inguinal and right internal iliac nodes (2-3 cm in size).

Treatment	Rating	Comments
Chemotherapy alone	2	
Immunotherapy alone	5	
Chemotherapy and immunotherapy	4	
Radioimmunotherapy alone	2	
Chemotherapy and immunotherapy followed by IFRT (24–30 Gy)	5	
Immunotherapy followed by IFRT (24–30 Gy)	4	
Observation	4	
Radiation Therapy Alone		
24–30 Gy	8	
36–45 Gy	3	Doses >36 Gy carry the potential for bowel toxicity.
4 Gy	4	
Extended field radiotherapy (EFRT)	1	
Involved field radiotherapy (IFRT)	8	
Involved node radiotherapy (INRT)	3	Usually considered after immunotherapy or chemotherapy.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 35-year-old woman with stage IA follicular lymphoma (grade 1) involving a single 2.8 cm lymph node in the axilla that was removed at the biopsy with no evidence of residual adenopathy.

Treatment	Rating	Comments
Chemotherapy alone	2	
Immunotherapy alone	3	
Chemotherapy and immunotherapy	3	
Radioimmunotherapy alone	2	
Chemotherapy and immunotherapy followed by IFRT (24–30 Gy)	2	
Immunotherapy followed by IFRT (24–30 Gy)	3	
Observation	7	
Radiation Therapy Alone		
24–30 Gy	7	
36–45 Gy	3	Doses >36 Gy carry the potential for toxicity.
4 Gy	2	
Extended field radiotherapy (EFRT)	2	
Involved field radiotherapy (IFRT)	7	
Involved node radiotherapy (INRT)	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 80-year-old symptomatic woman with stage IIB bulky (12 cm) follicular lymphoma involving the mesentery and para-aortics.

Treatment	Rating	Comments
Chemotherapy alone	3	Intensity of chemotherapy will depend on performance status and comorbidities.
Immunotherapy alone	4	
Chemotherapy and immunotherapy	7	Intensity of chemotherapy will depend on performance status and comorbidities.
Radioimmunotherapy alone	3	
Chemotherapy and immunotherapy followed by IFRT (24–30 Gy)	8	Radiotherapy dose and volume will be influenced by comorbidities.
Immunotherapy followed by IFRT (24–30 Gy)	5	
Observation	1	
Radiation Therapy Alone		
24–30 Gy	6	May be more appropriate if patient is unable to tolerate chemotherapy or immunotherapy.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
36–45 Gy	6	Doses >36 Gy carry the potential for bowel toxicity.
4 Gy	6	If patient has poor performance status and is unable to tolerate more intensive therapy, this may be appropriate.
Extended field radiotherapy (EFRT)	2	
Involved field radiotherapy (IFRT)	7	
Involved node radiotherapy (INRT)	6	

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 50-year-old man with chemotherapy- and immunotherapy-refractory stage IV follicular lymphoma with a 6 cm para-aortic nodal mass causing significant back pain.

Treatment	Rating	Comments
Chemotherapy alone	2	
Immunotherapy alone	2	
Chemotherapy and immunotherapy	2	
Radioimmunotherapy alone	3	
Chemotherapy and immunotherapy followed by IFRT (24–30 Gy)	3	
Immunotherapy followed by IFRT (24–30 Gy)	3	
Observation	1	
Radiation Therapy Alone		
24–30 Gy	8	
36–45 Gy	6	Doses >36 Gy carry the potential for toxicity.
4 Gy	7	
Extended field radiotherapy (EFRT)	2	
Involved field radiotherapy (IFRT)	7	
Involved node radiotherapy (INRT)	8	

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction

Patients with indolent lymphomas are predominantly found to have advanced-stage disease (stage III and IV) at diagnosis. Although effective

therapies exist for patients found to have early-stage disease (stage I or II, nonbulky), the patients with advanced disease are incurable. Fortunately, the typical slow progression of indolent lymphomas, even with observation alone, and their high responsiveness to a number of different therapeutic agents, translates into longer survival times compared with most other malignancies.

Epidemiology

An estimated 70,000 people were diagnosed with non-Hodgkin lymphoma (NHL) in the United States in 2012, which will result in close to 20,000 deaths. Indolent lymphomas make up over 35% of NHL cases, of which two-thirds are follicular lymphoma and the remainder include small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) and marginal zone lymphoma.

The average age at diagnosis is approximately 60 years, and indolent lymphoma is rarely diagnosed in children. There is a slight male predominance (1.2:1) of follicular lymphoma and a higher predominance amongst whites (white-to-black, 2.5:1; white-to-Asian, 2.4:1). Additionally, a higher incidence has been noted in families of patients with follicular lymphoma.

Pathology, Immunophenotype, and Genetics

Follicular lymphoma is graded according to the extent to which large centroblasts are visible in the biopsy:

- Grade 1: 0 to 5 centroblasts/high-power field (hpf); ~50% of cases
- Grade 2: 6 to 15 centroblasts/hpf; ~30% of cases
- Grade 3: >15 centroblasts/hpf; ~20% of cases
  Grade 3 can be divided into grade 3a, with centrocytes present, and grade 3b, with solid sheets of centroblasts. Grade 3 follicular lymphoma behaves more like aggressive NHL, and its treatment therefore follows the same guidelines as those used for a diffuse large B-cell lymphoma.

Follicular lymphomas express pan–B-cell antigens (CD19, CD20, CD22) and lack T-cell antigens (CD5, CD43). Approximately 85% of follicular lymphoma patients have a chromosomal translocation, t(14;18)(q32;q21), which results in an upregulation of the BCL-2 oncogene.

Presentation and Staging

Patients typically present with painless peripheral adenopathy that may wax and wane in size. Classical B symptoms, including fevers, drenching night sweats, or unintentional weight loss of >10% in the 6 months before presentation, occur in about 20% of patients.

Follicular lymphoma is staged by the Ann Arbor system used for other lymphomas. Distribution by stage is approximately 17% for stage I, 15% for stage II, 30% for stage III, and 37% for stage IV. It is critical to perform a careful physical examination of all the lymph node regions, including the liver (involved in up to 50% of cases) and spleen (involved in up to 40% of cases). Important tests to order include a complete blood count, liver function tests, lactate dehydrogenase (LDH), bone marrow biopsy (involved in up to 60%–70% of cases), and a computed tomography (CT) scan of the neck, chest, abdomen, and pelvis. Additional fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scans may be useful in confirming localized involvement (stage I and II) and for radiotherapy (RT) treatment planning. In one study, 42 patients with stage I/II follicular lymphoma staged by physical examination, CT, and bone marrow biopsy underwent FDG-PET imaging to evaluate the additional impact it would have on staging. Of these patients, 31% were upstaged to either stage III or IV, which would have led to a change in management from involved field radiation therapy (IFRT) to either expectant management or systemic therapy. An additional 14% of patients were found to have more sites of nodal disease without having stage III or IV disease, and thus required more IFRT than previously anticipated. In a similar study 45 patients with follicular lymphoma underwent CT and PET/CT staging. PET imaging increased the Ann Arbor staging in 18% of patients, including 11% who were upstaged from stage I or II disease to stage III or IV and were thus not eligible for curative treatment with RT. Upstaging patients with PET imaging can impact not only current and future studies but also how older pre–PET-era studies that report on treatment outcomes in patients with stage I and II disease are evaluated.

Follicular Lymphoma International Prognostic Index (FLIPI)

Follicular lymphoma has its own prognostic index: the Follicular Lymphoma International Prognostic Index, or FLIPI. The FLIPI includes five risk factors and comprises a low-risk group (no more than 1 factor), an intermediate-risk group (2 factors), and a high-risk group (3 or more factors). The 5 factors are: age ≥60 years, stage III or IV, hemoglobin level <12 g/dL, serum LDH > upper limit of normal, and number of involved nodal sites (not per Ann Arbor) ≥5. For the low-, intermediate-, and high-risk groups, the 10-year overall survival (OS) rates are 71%, 51%, and 26%, respectively. The FLIPI has been validated in patients diagnosed with early-stage disease where it was demonstrated that patients with two factors had a worse outcome than those with no more than one factor, including median failure-free survival time (11.1 years versus 2.4 years; P=0.02) and median OS time (not reached versus 7.4 years; P=0.01). Additionally, the FLIPI has been validated in patients undergoing rituximab and chemotherapy, and has been validated for predicting risk of transformation. Recently a newer prognostic index was developed, FLIPI2. The risk factors it includes are: beta-2-microglobulin level, longest diameter of lymph node involvement (>6 cm), bone marrow involvement, hemoglobin

level <12 g/dL, and age >60 years; FILIPI2 has been shown to be predictive of progression-free survival (PFS) and OS times.

Transformation into Aggressive Non-Hodgkin Lymphoma

Histologic transformation from an indolent lymphoma into an aggressive NHL is most commonly seen in follicular lymphoma transforming into diffuse large B-cell lymphoma. Studies have reported incidences between 15% and 30% at 10 years following initial diagnosis of the indolent lymphoma. Little is currently understood about the events leading to transformation. Treatment is directed based on newly transformed histology with median survival times of 1 to 2 years.

Early-Stage Follicular Lymphoma

Late relapses and the rarity of early-stage follicular lymphoma make phase III studies difficult to conduct. Therefore, the array of treatments delivered at both academic and community practices varies widely. In a recent report from the National LymphoCare Study, a multicenter, longitudinal observational study including both community and academic practices, of 474 patients with stage I follicular lymphoma, 29% underwent observation alone, 23% received RT alone, 35% received rituximab alone or with chemotherapy, and 8% received rituximab with or without chemotherapy followed by RT. Preliminary analysis of patients with stage I disease in this study (median follow-up of 4.75 years) suggests that similarly excellent early outcomes can be achieved with a variety of treatment approaches. (See Variants 1, 2, and 3.)

Surveillance

Although typically used to manage patients with incurable stage III or IV disease, surveillance has been used in some cases of curable stage I and II disease. One retrospective study reported on 43 patients with stage I or II follicular lymphoma diagnosed between 1969 and 2000 who underwent surveillance due to concerns regarding toxicity from RT alone (n=16), advanced age, or comorbidities (n=10), or patient or physician preference (n=17). Of note, these patients were not part of a prospective surveillance study, and patients who progressed in the 3 months following diagnosis were excluded from this study. Of the study patients, 63% never required treatment; however, 37% did require treatment (median time to treatment, 22 months) due to progressive disease (n=12) or transformed disease (n=4). All 9 deaths occurred among the 16 patients who required treatment. Although this study demonstrated that not everyone with early-stage disease requires treatment, there are currently no clear guidelines to distinguish these patients from those who progress during observation. Considering the high death rate among those who progressed and required treatment, active surveillance should be reserved for select patients who are not eligible for definitive treatment with RT.

Surgery

In patients with limited stage I disease, diagnostic surgery may eradicate all evidence of gross disease. One study reported on 26 patients who had complete eradication of their lymphoma from the diagnostic surgery and who underwent close observation. During follow-up, 13 of the patients relapsed, with a 5-year PFS rate of 53% and a 10-year PFS rate of 27%. Six of the relapses occurred locally, but only half were salvaged with RT. No local failures occurred among 17 additional patients who received IFRT and were studied in parallel with those who had undergone close observation. Additionally, only 2 patients among the 17 treated died during follow-up, while 7 among those who underwent close observation died.

Radiotherapy

Several studies have described the outcomes for patients with early-stage follicular lymphoma treated with RT alone. Appendix 1 in the original guideline document reviews the outcomes for several of these studies, demonstrating 10-year PFS rates of approximately 50% and OS rates of 60% to 70%. When evaluating these studies, one must keep in mind that they were done prior to the use of PET imaging for staging. PET imaging may facilitate disease control after RT alone by improving patient selection and target volume delineation.

In one of the largest studies, Stanford University (Palo Alto, CA) reported on 177 patients treated with RT between 1961 and 1994 for stage I and II low-grade follicular lymphoma. Various radiation techniques and doses were used during the different time periods covered in the study. Patients received IFRT, extended field radiation therapy (EFRT), total lymphoid irradiation (TLI), or sub-TLI (STLI) to doses of 35 Gy to 50 Gy at 1.5 Gy to 2.5 Gy per fraction. With a median follow-up of 7.7 years, the median OS time was 13.8 years with a 10-year freedom from recurrence rate of 44% and an OS rate of 64%. In the experience of Princess Margaret Hospital (Toronto, Ontario) treating 190 patients with stage I or II follicular lymphoma, definitive treatment with RT (with variations in radiation field designs and doses) led to a 12-year relapse-free survival rate of 53%, a cause-specific survival rate of 67%, a local relapse-free survival rate of 87%, a distant relapse-free survival rate of 62%, and an OS rate of 58%. Additionally, it was noted that the relapses usually occurred at unirradiated sites. Lastly, a large study from the British National Lymphoma Investigation reported on the outcomes of 208 patients with low-grade stage I disease treated with RT alone between 1974 and 1991 (radiation fields were not described, but a dose of 35 Gy was suggested). The OS rate at 10 years was 64% and the cancer-specific survival rate was 71%.

Considering the infrequency of early-stage follicular lymphoma and the need for single institutions to include 20 to 30 years' worth of patients in their studies to provide an adequate cohort, studies that include large databases can be helpful. One research group recently reported on the outcomes of 6,568 patients with stage I and II grade 1 and 2 follicular lymphoma diagnosed between 1973 and 2004 who were registered in the Surveillance Epidemiology and End Results (SEER) registry. During the 30-year study period, approximately one-third of patients received upfront RT. Due to limitations of the SEER database, information regarding radiation field design, radiation dose, and the use of chemotherapy or immunotherapy is not known. Researchers found that the 10-year disease-specific and OS rates were higher in patients who received RT as part of their treatment than in patients who did not receive RT (79% versus 66%, P<0.0001, and 62% versus 48%, P<0.0001, respectively). Although any SEER analysis has a number of weaknesses for the reasons given, the outcomes do coincide with those seen in other studies. Nevertheless, the magnitude of difference between the 2 groups may, in part, be due to likely selection bias of observation or chemotherapy alone in patients with significant comorbidities compared with patients who receive RT (see Appendix 1 in the original guideline document).

Chemotherapy and Radiotherapy

Studies regarding treatment regimens for localized low-grade NHL that combine chemotherapy and RT have generally included few patients and have shown conflicting results. Still, two studies did have reasonable patient numbers for evaluation. In a randomized study by the British National Lymphoma Investigation group in which 148 patients were randomly assigned to RT either with or without adjuvant chlorambucil with a minimum follow-up of 11 years, no differences were seen in OS (P>0.1) or relapse-free survival (P=0.14). In another study of 102 patients with stage I/II low-grade lymphoma, treatment consisted of 10 cycles of cyclophosphamide, vincristine, prednisone, and bleomycin, with or without doxorubicin, followed by 30 Gy to 40 Gy of IFRT. After a median follow-up of 10 years, the relapse-free and OS rates at 10 years were 76% and 82%, respectively. Late toxicities, however, did include 2 patients with leukemia and 12 patients with solid cancers (4 with cancers within the RT field). In the LymphoCare database, 26 patients who were rigorously staged and found to have stage I disease received systemic therapy and RT, demonstrating that this regimen has been adopted by some oncologists, especially in patients with grade 3 histology and those with B symptoms.

Radiotherapy Dose

Studies evaluating the use of RT in patients with early-stage indolent lymphoma have typically used radiation doses between 20 Gy and 50 Gy. Although retrospective studies have demonstrated that lower radiation doses appeared to be as effective as higher doses, a recent phase III randomized study from the United Kingdom tested the results of 24 Gy versus 40 Gy to 45Gy. Two hundred and eighty-nine patients with 361 sites of indolent lymphoma were randomized. The results demonstrated no difference in overall response rate between the standard-dose (93%) and lower-dose (92%) arms. With a median follow-up of 5.6 years, there was no significant difference in the rate of within-radiation field progression (hazard ratio [HR] = 1.09, 95% confidence interval [CI] = 0.76–1.56; p = 0.64) nor in the PFS or OS. In a subset analysis of 248 patients who received radical RT as first-line therapy, there was no difference in PFS, with 54% in the high-dose arm and 64% in the 24 Gy arm remaining alive without recurrence at any site at last follow-up. Thus, lower doses of 24 Gy to 30 Gy are generally preferred due to the anticipated lower risk of radiation-induced acute and late toxicity.

Radiotherapy Field Size

Treatment fields for the management of indolent lymphoma have ranged from total body irradiation (TBI) to TLI, to EFRT, to IFRT, and most recently to a tailored field (see Appendix 1 in the original guideline document). Owing to improvements in staging and concern for radiation toxicity, the standard field size for the last 20 years has been IFRT. A recent retrospective study evaluated the impact of an involved regional RT field (142 patients; 60%) compared with a tailored field that included the involved node with up to a 5 cm margin (95 patients; 40%). At 10 years, the PFS rate was 49% and the OS rate was 66% with no difference between the 2 groups. Furthermore, after receiving radiation to the tailored field, 1% of patients had a regional-only recurrence.

Recently, a new set of field designs, the involved-site radiation therapy (ISRT) fields, have been developed and endorsed by the steering committee of the International Lymphoma Radiation Oncology Group (ILROG). Led by experienced radiation oncologists specializing in lymphoma who initially organized the standardization of IFRT fields in the 2-dimensional (2-D) era a decade ago, the ISRT fields are a "modernized" version of IFRT fields. These new field designs were developed to take into consideration modern technology, including the use of staging PET/CT scans, 3-dimensional (3-D) and 4-dimensional (4-D) treatment planning with CT scanners, and conformal treatment techniques, as well as the use of image guidance, in order to replace the antiquated IFRT fields that were based on 2-D treatment planning and bony anatomy. These new fields are expected to be somewhat smaller than the traditional IFRT fields, but bigger than the involved node radiation therapy (INRT) fields. A more detailed description of the ISRT field design is expected to be published in the near future, and early descriptions can be found in the 2013 National Comprehensive Cancer Network (NCCN) guidelines for Hodgkin lymphoma.

Advanced-Stage Follicular Lymphoma

The management of patients with more advanced disease, including stage IIB bulky, stage III, and stage IV, is quite controversial. Options that have been used and studied in the past include surveillance, radiation (low-dose TBI or TLI), immunotherapy (rituximab), chemotherapy (e.g.,

bendamustine [cyclophosphamide, doxorubicin, vincristine, prednisone], CVP [cyclophosphamide, vincristine, prednisone], fludarabine), or some combination of the agents.

Indications for treatment may include symptomatic disease, threatened end-organ function, cytopenia due to lymphoma involvement, bulky disease, progressing disease, patient preference, or a combination of these factors. Currently, systemic therapies are preferred to EFRT in the management of advanced-stage disease out of concerns for acute and late RT toxicity; however, localized palliative RT may be helpful in patients unsuitable for systemic therapy (see Variant 4, above).

Relapsed and Refractory Disease

The management of relapsed and refractory disease is similar to that used for advanced-stage disease and includes a combination of immunotherapy with chemotherapy. In addition to systemic chemotherapy, options may include radioimmunotherapy (ibritumomab, tiuxetan or tositumomab), high-dose therapy with autologous stem cell rescue, an allogeneic stem cell transplant, or palliative RT, all of which confer reasonable response rates (see Variant 5, above).

Palliative Radiation Therapy

The radiosensitivity of indolent lymphoma has been recognized for years. A prospective study of patients with advanced follicular lymphoma randomized patients to single-alkylating-agent chemotherapy (cyclophosphamide or chlorambucil), CVP chemotherapy, or whole-body irradiation (WBI) at 30 cGy per day, 2 to 3 times per week, to a total dose of 150 cGy (with a boost of 20 Gy in 2 to 3 weeks to sites of initial involvement). The investigators reported a 5-year relapse-free survival rate of 35% following WBI. In Europe, after several patients responded early in their treatment course, either after a few fractions of radiation or when they prematurely stopped their planned RT, investigators became interested in prospective studies of low-dose palliative RT to localized sites. In the largest multicenter phase II study evaluating palliative RT for indolent lymphoma, 109 patients with a total of 304 symptomatic sites of recurrent indolent lymphoma were irradiated with 4 Gy either over 2 fractions or in a single fraction to either the entire lymph node region or the lymph node with a 1.5 cm margin. The overall response rate was 92%, with a median duration time until local relapse of 25 months and time to any progression of 14 months. Other single-institution studies have also demonstrated similar results following low-dose palliative RT with median local control times of 1 to 2 years (see Appendix 2 in the original guideline document).

Radiation Therapy Techniques

Considering the involved sites at presentation and the relatively low dose of RT needed for disease control, the most basic treatment planning is acceptable, using a CT simulation for 3-D conformal radiotherapy (3-D CRT) planning with an anterior-posterior/posterior-anterior field arrangement. For some patients, however, a more complex 3-D CRT plan, an intensity-modulated radiation therapy (IMRT) plan, or even a proton therapy plan should be considered to minimize dose to critical normal structures. If using more conformal techniques, one should keep in mind that data about them are limited, and further clinical studies are needed. Furthermore, one should consider the impact of radiation dose uncertainty and the potential impact of irradiating more tissue with low-dose radiation.

Summary

- Localized indolent nodal lymphoma is a rare diagnosis.
- FDG-PET/CT scans can demonstrate more disseminated disease and upstage patients thought to have localized involvement. Additionally, they can be useful in RT treatment planning.
- Based on a number of prospective and retrospective studies of patients treated with RT alone, the 10-year PFS and OS rates are expected to be approximately 50% and 65%, respectively.
- Definitive treatment with RT should include the use of IFRT and doses between 24 and 30.6 Gy.
- Advanced radiation techniques, such as IMRT and proton therapy, may be considered depending on the clinical scenario and whether an improvement in the therapeutic ratio is expected.
- Observation can be considered in specialized cases, where the risk from treatment outweighs the benefits.
- For patients with more advanced stage II disease, such as bulky disease and B-symptoms, a more aggressive approach including chemotherapy, immunotherapy, and RT, should be considered.
- Patients with advanced stage disease refractory to chemotherapy and immunotherapy can sustain long intervals of local control with low-dose palliative RT of 4 Gy.

Abbreviations

- EFRT, extended field radiotherapy
- IFRT, involved field radiotherapy

- INRT, involved node radiotherapy

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Localized nodal indolent lymphoma

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Hematology

Oncology

Radiation Oncology

Radiology

Surgery

Intended Users

Health Care Providers

Health Plans

Hospitals

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of radiologic examinations and treatment procedures for localized nodal indolent lymphoma

Target Population

Patients with localized indolent nodal lymphoma

Interventions and Practices Considered

1. Chemotherapy alone
2. Immunotherapy alone
3. Chemotherapy and immunotherapy
4. Radioimmunotherapy alone
5. Chemotherapy and immunotherapy followed by involved field radiotherapy (IFRT)
6. Immunotherapy followed by IFRT
7. Observation
8. Radiation therapy alone
   - Radiation dose ranges
   - Extended field radiotherapy (EFRT)
   - IFRT
   - Involved node radiotherapy (INRT)

Major Outcomes Considered

- Utility of radiologic examinations in the evaluation and staging of localized nodal indolent lymphoma
- Survival times (progression-free and overall)
- Disease progression
- Time to local progression
- Complete and partial response rates
- Treatment-related toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Procedure

Staff will search in PubMed only for peer reviewed medical literature for routine searches. Any article or guideline may be used by the author in the narrative but those materials may have been identified outside of the routine literature search process.

The Medline literature search is based on keywords provided by the topic author. The two general classes of keywords are those related to the condition (e.g., ankle pain, fever) and those that describe the diagnostic or therapeutic intervention of interest (e.g., mammography, MRI).

The search terms and parameters are manipulated to produce the most relevant, current evidence to address the American College of Radiology Appropriateness Criteria (ACR AC) topic being reviewed or developed. Combining the clinical conditions and diagnostic modalities or therapeutic procedures narrows the search to be relevant to the topic. Exploding the term "diagnostic imaging" captures relevant results for diagnostic topics.

The following criteria/limits are used in the searches.

1. Articles that have abstracts available and are concerned with humans.
2. Restrict the search to the year prior to the last topic update or in some cases the author of the topic may specify which year range to use in the search. For new topics, the year range is restricted to the last 10 years unless the topic author provides other instructions.
3. May restrict the search to Adults only or Pediatrics only.
4. Articles consisting of only summaries or case reports are often excluded from final results.

The search strategy may be revised to improve the output as needed.

Number of Source Documents

The total number of source documents identified as the result of the literature search is not known.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Strength of Evidence Key

Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.

Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.

Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.

Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author drafts or revises the narrative text summarizing the evidence found in the literature. American College of Radiology (ACR) staff draft an evidence table based on the analysis of the selected literature. These tables rate the strength of the evidence (study quality) for each article included in the narrative text.

The expert panel reviews the narrative text, evidence table, and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the table. Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The appropriateness ratings for each of the procedures included in the Appropriateness Criteria topics are determined using a modified Delphi methodology. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. American College of Radiology (ACR) staff distribute surveys to the panelists along with the evidence table and narrative. Each panelist interprets the available evidence and rates each procedure. The surveys are completed by panelists without consulting other panelists. The appropriateness rating scale is an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate"; 4, 5, or 6 are in the category "may be appropriate"; and 7, 8, or 9 are in the category "usually appropriate." Each panel member assigns one rating for each procedure for a clinical scenario. The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying

which members provided any particular rating.

If consensus is reached, the median rating is assigned as the panel's final recommendation/rating. Consensus is defined as eighty percent (80%) agreement within a rating category. A maximum of three rounds may be conducted to reach consensus. Consensus among the panel members must be achieved to determine the final rating for each procedure.

If consensus is not reached, the panel is convened by conference call. The strengths and weaknesses of each imaging procedure that has not reached consensus are discussed and a final rating is proposed. If the panelists on the call agree, the rating is proposed as the panel's consensus. The document is circulated to all the panelists to make the final determination. If consensus cannot be reached on the call or when the document is circulated, "No consensus" appears in the rating column and the reasons for this decision are added to the comment sections.

This modified Delphi method enables each panelist to express individual interpretations of the evidence and his or her expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. A more detailed explanation of the complete process can be found in additional methodology documents found on the ACR Web site _____ (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate treatment procedures for localized nodal indolent lymphoma

Potential Harms

Radiation-induced and chemotherapy-related toxicities (acute and late)

Qualifying Statements

Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Hoppe BS, Constine LS, Hodgson DC, Advani R, Dabaja BS, Flowers CR, Ha CS, Metzger ML, Plastaras JP, Roberts KB, Shapiro R, Terezakis SA, Winkfield KM, Younes A, Expert Panel on Radiation Oncology€"Lymphoma. ACR Appropriateness Criteria® localized nodal indolent lymphoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2013. 13 p. [46 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Lymphoma

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site _____.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site _____.
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2013 Apr. 1 p. Electronic copies: Available in PDF from the ACR Web site _____.
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available in PDF from the ACR Web site _____.
- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available in PDF from the ACR Web site _____.
- ACR Appropriateness Criteria® localized nodal indolent lymphoma. Evidence table. Reston (VA): American College of Radiology; 2013.

19 p. Electronic copies: Available from the ACR Web site [   ].

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on March 12, 2014. This summary was updated by ECRI Institute on March 19, 2015 following the U.S. Food and Drug Administration advisory on Treanda (bendamustine hydrochloride).

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